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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/527,598	11/03/2005	Pierrette Gaudreau	AKL-001	7604

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EXAMINER	
BRADLEY, CHRISTINA	

ART UNIT	PAPER NUMBER
1654	

NOTIFICATION DATE	DELIVERY MODE
05/13/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/527,598	GAUDREAU, PIERRETTE	
	Examiner	Art Unit	
	CHRISTINA BRADLEY	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 February 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *48 and 81-97* is/are pending in the application.

4a) Of the above claim(s) *94,96 and 97* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *48,81-93 and 95* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/15/2008, 1/23/2009, 02/03/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Claims 48 and 81-97 are pending. Claims 1-47 and 49-80 are cancelled; **all objections to and rejections of these claims are now moot**. Claims 81-97 were newly added in the response filed 11/10/2008. Applicant's election of the species pharmaceutical composition in a formulation suitable for injection **without** traverse in the reply filed on 02/17/2009 is acknowledged. Prior art was found on this species which reads on claim 91 and additionally on topical, inhalation and oral administration which read on claims 92, 93 and 95, respectively. In accordance with MPEP § 803.02 the search was not extended. Claims 94, 96 and 97 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim.

Information Disclosure Statement

2. The information disclosure statements (IDS) submitted on 11/15/2008, 01/23/2009 and 02/03/2009 was filed after the mailing date of the first action on the merits on 09/24/2007. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements are being considered by the examiner. However, the foreign patent documents CA 2377339 (cited on 11/15/2008) and WO 91/16923 (cited 01/23/2009) have not been considered because a legible copy of each was not submitted in accordance with 37 CFR 1.98(a)(2).

Claim Objections

3. The objection to claim 48 to for the use of the acronym GHRH is withdrawn.

4. The objection to claim 48 for the spacing in the formula is withdrawn.

5. The objection to claim 48 for the use of "pharmaceutical acceptable salt" is withdrawn.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 48 and 92 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gaudreau (U.S. Patent No. 5,854,216, cited reference A1 on the Information Disclosure Statement filed 2/7/2007). Gaudreau teaches a GHRH analogue consisting of:

Tyr-D-Ala^{2}-Asp-Ala-Ile-Phe-Thr-Asn-Ser- D-Tyr^{10}-Arg-Lys-Val-Leu-D-Ala^{15}-Gln-Leu-Ser-Ala-Arg-Lys^{21}-Lys^{22}-Leu-Gln-Asp-Ile-Met-Ser-Arg-NH_2

wherein A2 is D-Ala, A8 is Asn, A10 is D-Tyr, A15 is D-Ala, A21 is Lys, A22 is Lys and A30 is a bond (Tables 10 and 11, compound 8). Gaudreau teaches that this peptide was synthesized using solid-phase methods (final solvents and conditions were not reported) and added in increasing concentrations (0 to 1000 nM) to anterior pituitary homogenates in 300 μl of Tris-HCl buffer, pH 7.4, containing 5 mM EDTA, 5mM MgCl2 and 0.42% BSA (col 12, lines 51-67).

8. Gaudreau does not explicitly teach that this GHRH analogue was formulated in a pharmaceutical composition.

9. It would have been obvious to make this GHRH analogue and to dissolve it in a pharmaceutically-acceptable carrier at a concentration effective to stimulate secretion or synthesis of growth hormone. The skilled artisan would have been motivated to do so based on the teaching of Gaudreau that the GNRH analogue above possesses biological activity, a binding

affinity to the receptor in rat adenopituitary cells equivalent to that of wild type hGRF(1-29)NH_2 (Table 11), and that related peptides can be used to treat a variety of conditions such as hypothalamic pituitary dwarfism, burns, osteoporosis, renal failure, non-union-bone fracture, wounds, post-surgical problems, lactation failure, female infertility, cachexia, T-cell immunodeficiencies, neurodegenerative conditions and GRF receptor-dependent tumors (claim 3). The skilled artisan would have been further motivated to combine the peptide with a pharmaceutically acceptable carrier suitable for the specific condition to be treated and the desired mode of administration. With respect to claim 92, the mode of administration for burns would be topical. There would have been a reasonable expectation of success given that the GHRH analogue peptides can be synthesized using solid state methods, and formulated in pharmaceutically acceptable carriers, and that the GNRH analogue possesses biological activity.

10. In the response filed 11/10/2008, Applicant traverses the rejection on two grounds: 1) Gaudreau teaches away from the species recited in instant claim 48; and 2) Applicant has obtained unexpected and surprising results with respect to the species recited in instant claim 48. These arguments have been fully considered but are to found to be persuasive.

11. First, Applicant argues on pp. 9-10:

> Given that there are at least 30 peptides taught by Gaudreau (see for example, claim 3 of Gaudreau), it would be reasonable to assume that some sort of criteria would be used to identify which of the peptides should undergo further testing. As has been previously noted, compound 8 is not even among those peptides that are further tested for their ability to activate adenylate cyclase activity in cultured cells (see Gaudreau, Table 12, Col. 27, and text corresponding thereto). Based on the initial testing with rat adenopituitary cells Gaudreau appears to teach away from the use of compound 8. Specifically, compound 8 was not deemed promising enough to undergo further testing. Gaudreau does not even claim a therapeutic use for Ra-X-Rb compound comprising compound 8 in claims 3 or 4.

The fact that compound 8 is one of 30 peptides taught by Gaudreau and was not selected by Gaudreau for further testing or for inclusion in the patent claims does not constitute a clear teaching away from this species. MPEP § 2123(II) states: "Disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. *In re Susi*, 440 F.2d 442, 169 USPQ 423 (CCPA 1971). "A known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same use." *In re Gurley*, 27 F.3d 551, 554, 31 USPQ2d 1130, 1132 (Fed. Cir. 1994)" Based on the data in Table 11, the skilled artisan would conclude that compound 8 possesses an inferior binding affinity for the rat adenopituitary to compounds 6, 7, 10, 11, 13 and 14, a superior binding affinity for the rat adenopituitary to compounds 2-5, 9 and 12, and a comparable binding affinity for the rat adenopituitary to the wild-type hGRF(1-29)NH_2 peptide. There is nothing in Gaudreau to suggest that a binding affinity for the rat adenopituitary comparable to that of wild-type hGRF(1-29)NH_2 is undesirable or would result in deleterious effects *in vivo*. The fact that compound 8 was not selected for further testing in the adenylate cyclase assay (Table 12) is not significant given that the compounds selected for further testing included those that exhibited both low binding affinity in the rat adenopituitary assay (compounds 2, 5 and 9) and those that exhibited high binding affinity in the rat adenopituitary assay (compounds 10, 11 and 6). The fact that compound was excluded from claims 3 and 4 is not significant because the factors that lead to a claim limitation being included and removed from a claim over the course of prosecution are varied and complex and may or may not relate to the issues under consideration in this rejection. Furthermore, Gaudreau teaches

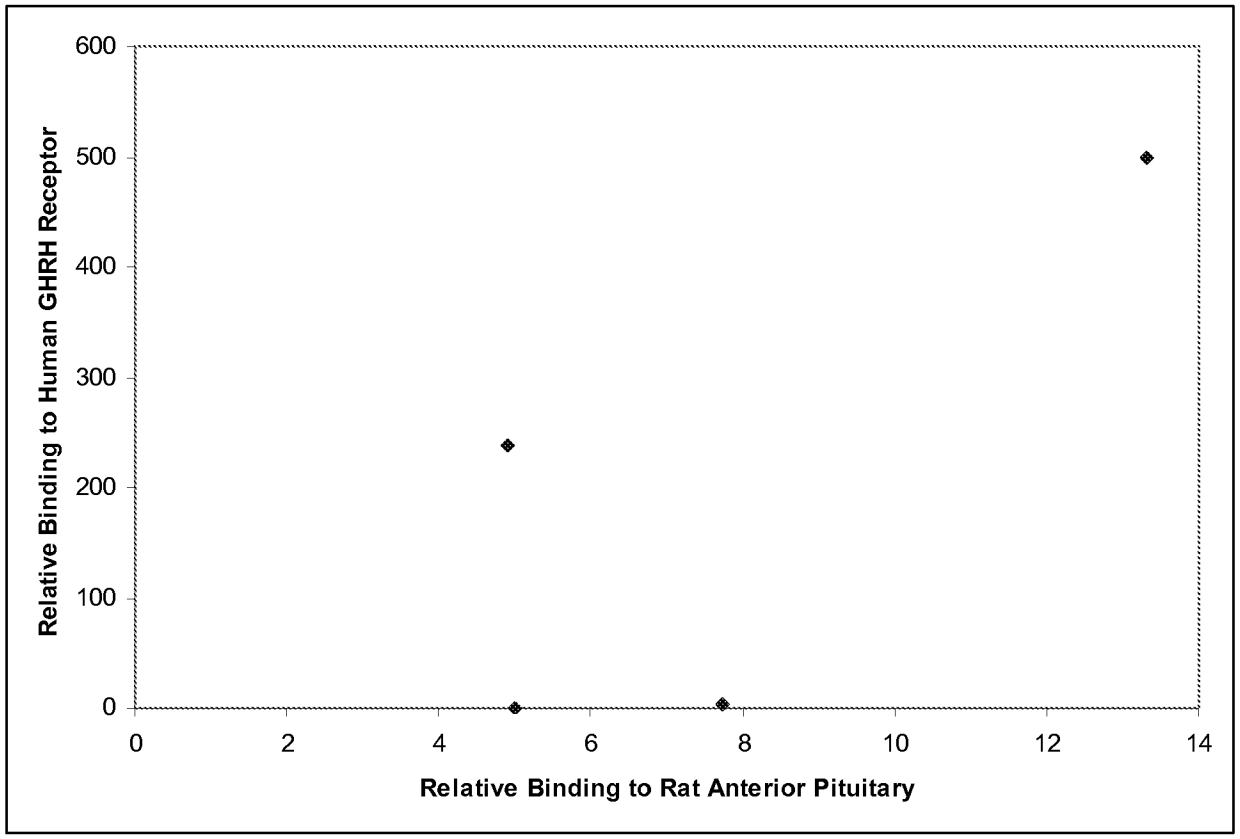
that the peptides disclosed have utility for the treatment of a variety of conditions related to growth hormone (col 5, lines 12-37).

12. Second, Applicant argues on pp. 8-9 that

> Applicants discovery that "the relative binding affinity of the synthetic peptides with the rat GHRH receptor is not predictive of the relative binding affinity with the human receptor" lead to the selection of the claimed GHRH analogue over many other analogues which, based on the teachings of Gaudreau, would appear to be more obvious for further testing.

Applicant argues that the lack of correlation between relative binding affinity of the GNRH analogues in the rat adenopituitary cells and the human GHRH receptor constitutes an unexpected and surprising result that overcomes the *prima facie* case of obviousness over Gaudreau. This is not found persuasive. MPEP § 716.02 states: "Any differences between the claimed invention and the prior art may be expected to result in some differences in properties. The issue is whether the properties differ to such an extent that the difference is really unexpected. *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986)" In the instant case, the premise of Applicant's argument seems to be that the skilled artisan would expect that GNRH analogues that exhibit low binding affinity to the rat adenopituitary cells would also exhibit low binding affinity to the human GHRH receptor, and that GNRH analogues that exhibit high binding affinity to the rat adenopituitary cells would also exhibit high binding affinity to the human GHRH receptor. It follows from this premise that compound 8 which exhibits low binding affinity to the rat adenopituitary cells should also exhibit low binding affinity to the human GHRH receptor and that therefore, Applicant's observation that compound 8 (compound 1 in the instant application) exhibits high binding affinity to the human GHRH receptor is a surprising and unexpected result. Applicant has not shown evidence that the

underlying premise of this argument is valid. If this premise were valid, one would expect for the compounds in Table 11 of Gaudreau, with the exception of compound 8 (compound 1 in the instant application), to follow this correlation. On the contrary, the data in Table 1 of the instant application does not follow this correlation; there is not a linear relationship between binding to the rat anterior pituitary and human GHRH receptor:



Therefore, Applicant has not provided evidence that the properties of the GNRH analogue recited in instant claim 48 are actually unexpected.

13. For these reasons, the rejection is maintained.

14. Claims 81-91, 93 and 95 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gaudreau (U.S. Patent No. 5,854,216, cited reference A1 on the Information Disclosure Statement filed 2/7/2007), as applied to claims 48 and 92 above, in further view of Seely et al. (U.S. Patent No. 5,137,872).

15. Gaudreau does not teach a pharmaceutical composition comprising sterile water, saline, buffered solution, diluents, stabilizers, preservatives, wetting agents, emulsifying agents, pH buffering agents, or viscosity enhancing agents or pharmaceutical compositions suitable for injection

16. Seely et al. teach a method for stimulating the release of GH in animals comprising administering to the animals an amount of the hGRF analogs sufficient to stimulate the release of GH. Seely e al. teach means of formulating the GRF analogues for administration.

17. It would have been obvious to formulate the GHRH analogues of Gaudreau according to the teaching of Seely et al. With respect to claim 81, Seely et al. teach combining the hGRF analogues with sterile aqueous solution (col 9, line 6). With respect to claim 82, Seely et al. teach the use of saline as a pharmaceutically acceptable carrier (col 11, lines 49-50). With respect to claim 83, Seely et al. teach the use of a buffered solution as a pharmaceutically acceptable carrier (col 11, lines 49-50, col 9, line 23). With respect to claim 84, Seely et al. teach that the pharmaceutical composition comprising hGRF analogues further comprises a diluent (col 8, line 44). With respect to claim 85, Seely et al. teach that the pharmaceutical composition comprising hGRF analogues further comprises a stabilizer (additives which enhance the stability, col 9, line 21). With respect to claim 86, Seely et al. teach that the pharmaceutical

composition comprising hGRF analogues further comprises a preservative (col 9, line 22). With respect to claims 87, 88 and 90, Seely et al. teach that the pharmaceutical composition comprising hGRF analogues further comprises a wetting agent, an emulsifying agent or a viscosity-enhancing agent such as ethanol, polyol (for example glycerol, propylene glycol, liquid polyethylene glycol), vegetable oils (for example, cottonseed oil, sesame oil, olive oil, soybean oil, corn oil, sunflower oil, or peanut oil), isopropyl myristate, parabens, chlorobutanol, phenol, sorbic acid, aluminum monostearate and gelatin (col 9, lines 4-35). With respect to claim 89, Seely et al. teach that the pharmaceutical composition comprising hGRF analogues further comprises a pH buffering agent (col 11, lines 49-50, col 9, line 23). With respect to claims 91, 93-95, Seely et al. teach that hGRF analogues may be administered nasally, orally or by injection such as by intravenous, intramuscular, subcutaneous, or intraperitoneal injection, or by subcutaneous implant (col 8, line 61 - col 9, line 3). The formulations taught by Seely et al. represent obvious variants of pharmaceutical formulations for GNRH analogues. Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Double Patenting

18. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

19. Claim 48 is provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 4 of copending Application No. 12/171,447. Although the conflicting claims are not identical, they are not patentably distinct from each other because claim 4 of copending Application No. 12/171,447 recites a pharmaceutical composition comprising the GHRH analog recited in instant claim 48, which anticipated instant claim 48. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

20. Claims 81-91, 93 and 95 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 4 of copending Application No. 12/171,447, as applied to claim 48 above, in further view of Seely et al. (U.S. Patent No. 5,137,872). The claims of copending Application No. 12/171,447 do not teach a pharmaceutical composition comprising sterile water, saline, buffered solution, diluents, stabilizers, preservatives, wetting agents, emulsifying agents, pH buffering agents, or viscosity enhancing agents or pharmaceutical compositions suitable for injection. Seely et al. teach a method for stimulating the release of GH in animals comprising administering to the animals an amount of the hGRF analogs sufficient to stimulate the release of GH. Seely e al. teach means of formulating the GRF analogues for administration. It would have been obvious to formulate the

GHRH analogue of copending Application No. 12/171,447 according to the teaching of Seely et al. With respect to claim 81, Seely et al. teach combining the hGRF analogues with sterile aqueous solution (col 9, line 6). With respect to claim 82, Seely et al. teach the use of saline as a pharmaceutically acceptable carrier (col 11, lines 49-50). With respect to claim 83, Seely et al. teach the use of a buffered solution as a pharmaceutically acceptable carrier (col 11, lines 49-50, col 9, line 23). With respect to claim 84, Seely et al. teach that the pharmaceutical composition comprising hGRF analogues further comprises a diluent (col 8, line 44). With respect to claim 85, Seely et al. teach that the pharmaceutical composition comprising hGRF analogues further comprises a stabilizer (additives which enhance the stability, col 9, line 21). With respect to claim 86, Seely et al. teach that the pharmaceutical composition comprising hGRF analogues further comprises a preservative (col 9, line 22). With respect to claims 87, 88 and 90, Seely et al. teach that the pharmaceutical composition comprising hGRF analogues further comprises a wetting agent, an emulsifying agent or a viscosity-enhancing agent such as ethanol, polyol (for example glycerol, propylene glycol, liquid polyethylene glycol), vegetable oils (for example, cottonseed oil, sesame oil, olive oil, soybean oil, corn oil, sunflower oil, or peanut oil), isopropyl myristate, parabens, chlorobutanol, phenol, sorbic acid, aluminum monostearate and gelatin (col 9, lines 4-35). With respect to claim 89, Seely et al. teach that the pharmaceutical composition comprising hGRF analogues further comprises a pH buffering agent (col 11, lines 49-50, col 9, line 23). With respect to claims 91, 93-95, Seely et al. teach that hGRF analogues may be administered nasally, orally or by injection such as by intravenous, intramuscular, subcutaneous, or intraperitoneal injection, or by subcutaneous implant (col 8, line 61 - col 9, line 3). The formulations taught by Seely et al. represent obvious variants of pharmaceutical formulations for

GNRH analogues. Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

21. No claims are allowed.

22. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

23. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

24. Any inquiry concerning this communication or earlier communications from the examiner should be directed to CHRISTINA BRADLEY whose telephone number is (571)272-9044. The examiner can normally be reached on Monday-Thursday, 8:30 A.M. to 4:30 P.M.

25. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

26. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Cecilia Tsang/
Supervisory Patent Examiner, Art Unit 1654

/Christina Marchetti Bradley/
Examiner, Art Unit 1654

cmb